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PATENT

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Charles K. Sholtz — 11-24-2003 (Date) — EU717459554US ("EXPRESS MAIL" Mailing Label Number)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Michael A. Sherman et al.

Application No.: 10/053,253

Filed: November 2, 2000

For: METHOD FOR LARGE TIMESTEPS IN MOLECULAR MODELING

Examiner: Carolyn L. Smith

Art Unit: 1631

RESPONSE TO RESTRICTION REQUIREMENT

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

AMENDMENT

Sir:

In response to the Office action mailed October 23, 2003, please amend the above-identified application as follows:

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 16 of this paper.

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

Claim 1 (currently amended): A method of modeling the behavior of a molecule, comprising

selecting a model for said molecule, said model having equations of motion for said molecule; and

integrating said model equations with a Radau5~~an L-stable~~ implicit integrator in large timesteps so as to obtain a calculations of said behavior of said molecule.

Claim 2 (original): The method of claim 1 wherein said large timesteps comprise intervals of at least 200 femtoseconds.

Claim 3 (original): The method of claim 2 wherein said integrating step is performed with varying timesteps.

Claim 4 (original): The method of claim 1 further comprising

correcting for errors in said integrating step to obtain a history of states of said molecule over time.

Claim 5 (original): The method of claim 1 wherein said selecting step includes selecting a stiff system model to obtain a history of states of said molecule over time.

Claim 6 (original): The method of claim 1 wherein said integrating step includes avoiding energy conservation to obtain a minimum energy state for said molecule.

Claim 7 (withdrawn): The method of claim 1 wherein said L-stable integrator comprises an integrator from the group comprising implicit Euler, Radau5, SDIRK3, SDIRK4, and other implicit Runge-Kutta methods.

Claim 8 (original): The method of claim 3 further comprising

correcting for errors in said integrating step to obtain a history of states of said molecule over time.

Claim 9 (original): The method of claim 3 wherein said selecting step includes selecting a stiff system model to obtain a history of states of said molecule over time.

Claim 10 (original): The method of claim 3 wherein said integrating step includes avoiding energy conservation to obtain a minimum energy state for said molecule.

Claim 11 (original): The method of claim 1 wherein said model is described in internal coordinates selected to speed calculations of said behavior of said molecule.

Claim 12 (original): The method of claim 11 wherein said model comprises a torsion angle, rigid body model of said molecule

Claim 13 (currently amended): A method of modeling the behavior of a molecule, comprising

selecting a model for said molecule, said model having equations of motion for said molecule;~~ and~~

selecting a Radau5~~an L-stable~~ integrator; and

integrating said model equations with said Radau5~~L-stable~~ integrator in timesteps of intervals varying over a range of at least 100 so as to obtain a calculation of said behavior of said molecule.

Claim 14 (original): The method of claim 13 wherein said timesteps comprise intervals of at least 200 femtoseconds.

Claim 15 (currently amended): The method of claim 14 wherein said Radau5~~L-stable~~ integrator is selected to remove energy from said model; and wherein said model equations are integrated without energy conservation to obtain a minimum energy state of said molecule.

Claim 16 (withdrawn): The method of claim 15 wherein said L-stable integrator comprises an implicit Euler integrator.

Claim 17 (original): The method of claim 14 wherein said model equations are integrated with error correction so as to obtain a history of states of said molecule over time.

Claim 18 (original): The method of claim 14 wherein said model is selected for stiff equations of motion so as to obtain a history of states of said molecule over time.

Claim 19 (original): The method of claim 14 wherein said model is selected for stiff equations of motion and said model equations are integrated with error correction, so as to obtain a history of states of said molecule over time.

Claim 20 (withdrawn): The method of claim 19 wherein said L-stable integrator comprises a Radau5 integrator.

Claim 21 (withdrawn): The method of claim 14 wherein said L-stable integrator is selected from the group comprising implicit Euler, Radau5, SDIRK3, SDIRK4 and implicit Runge-Kutta methods.

Claim 22 (original): The method of claim 14 wherein said model is described in internal coordinates selected to speed calculations of said behavior of said molecule.

Claim 23 (original): The method of claim 22 wherein said model comprises a torsion angle, rigid body model of said molecule.

Claim 24 (withdrawn): A method of modeling the behavior of a first molecule with a plurality of second molecules, comprising

selecting a first model for said first molecule, said model having equations of motion for said first molecule;

selecting a second model for each of said second molecules, said model having equations of motion for said second molecule;

selecting an L-stable integrator;

integrating said model equations with said L-stable integrator in timesteps of intervals varying in a range of at least 100 so as to obtain a calculations of said behavior of said first molecule with said plurality of second molecules.

Claim 25 (withdrawn): The method of claim 24 wherein said model equations are described in internal coordinates selected to speed calculations of said behavior.

Claim 26 (withdrawn): The method of claim 24 wherein said second molecule is selected from the group comprising salts, solvents, and other organic and inorganic compounds.

Claim 27 (withdrawn): The method of claim 26 wherein said second molecule comprises water.

Claim 28 (withdrawn): The method of claim 25 wherein said first molecule comprises a protein.

Claim 29 (withdrawn): The method of claim 25 wherein said large timesteps comprise intervals of at least 200 femtoseconds.

Claim 30 (withdrawn): The method of claim 29 wherein said L-stable integrator is selected to remove energy from said model; and wherein said model equations are integrated without energy conservation to obtain a minimum energy state of said molecule.

Claim 31 (withdrawn): The method of claim 30 wherein said L-stable integrator comprises an implicit Euler integrator.

Claim 32 (withdrawn): The method of claim 25 wherein said model equations are integrated with error correction so as to obtain a history of states of said molecule over time.

Claim 33 (withdrawn): The method of claim 25 wherein said model is selected for stiff equations of motion so as to obtain a history of states of said molecule over time.

Claim 34 (withdrawn): The method of claim 25 wherein said model is selected for stiff equations of motion and said model equations are integrated with error correction, so as to obtain a history of states of said molecule over time.

Claim 35 (currently amended): Computer code for modeling the behavior of a molecule on a computer, said code comprising

a first module defining a model for said molecule, said model including equations of motion for said molecule; and

a second module integrating said equations of motions with a Radau5~~an L-stable~~ implicit integrator to obtain calculations of said behavior of said molecule.

Claim 36 (original): The computer code of claim 35 wherein said second module integrates said equations of motion with varying timesteps.

Claim 37 (original): The computer code of claim 36 wherein said timesteps vary in magnitude over a range of at least 100.

Claim 38 (original): The computer code of claim 35 wherein said first module defines said model with internal coordinates.

Claim 39 (original): The computer code of claim 38 wherein said internal coordinates comprise generalized coordinates and generalized speeds.

Claim 40 (original): The computer code of claim 39 wherein said first module defines a rigid multibody, torsion-angle model for said molecule.

Claim 41 (withdrawn): A method of screening a library of compounds for interaction with a target, comprising

(a) selecting a model for the interaction of a compound with the target, the model having equations of motion for the compound and the target;

(b) inputting data for a first of the library of compounds into the equations of motions;

(c) integrating said model equations with an L-stable integrator in large time steps so as to obtain a calculation of the motions of the target and the compound and thereby the interaction of the compound with the target;

(d) repeating (b) and (c) for each compound in the library;

(e) comparing the interactions of the compounds with the target;

(f) synthesizing a compound selected based on its interaction with the target.

Claim 42 (withdrawn): The method of claim 41, wherein the library of compounds comprises a lead compound known to interact with the target and test compounds to be tested for interaction with the target.

Claim 43 (withdrawn): The method of claim 42, wherein the lead compound is a polypeptide and the test compounds are small molecules.

Claim 44 (withdrawn): The method of claim 43, wherein the lead compound is an antibody.

Claim 45 (withdrawn): The method of claim 42, wherein one of the compounds is a lead compound known to interact with the target and the comparing step compares the interactions between the test compounds and the target with that of the lead compound with the target to select a test compound having a similar interaction with the target to that of the lead compound.

Claim 46 (withdrawn): The method of claim 42, further comprising identifying the lead compound from a primary library by contacting the lead compound with the target and detecting interaction between the lead compound and the target.

Claim 47 (withdrawn): The method of claim 41, wherein different repetitions of steps (b) and (c) are performed on first and second compounds, the second compound being selected based on the interaction of the first compound with the target.

Claim 48 (withdrawn): The method of claim 41, further comprising testing the synthesized compound for interaction with the target.

Claim 49 (withdrawn): The method of claim 48, wherein the testing is performed in vitro, in a nonhuman animal or in a human.

Claim 50 (withdrawn): The method of claim 41, further comprising formulating the synthesized compound as a pharmaceutical composition.

Claim 51 (withdrawn): The method of claim 41, further comprising determining data relating to the structure of at least one of the library of compounds and/or the target.

Claim 52 (withdrawn): The method of claim 51, wherein the data are determined by X-ray crystallography.

Claim 53 (withdrawn): The method of claim 51, wherein the data are determined by infra red or ultraviolet spectroscopy, or NMR.

Claim 54 (withdrawn): The method of claim 41, wherein the compounds are selected from the group consisting of proteins, nucleic acids, polysaccharides, phospholipids, hormones, prostaglandins, steroids, and small molecules.

Claim 55 (withdrawn): The method of claim 54, wherein the compounds are small molecules selected from the group consisting of beta-turn mimetics, aromatic compounds,

heterocyclic compounds, benzodiazepines, oligomeric N-substituted glycines and oligocarbamates.

Claim 56 (withdrawn): The method of claim 41, wherein the target is selected from the group consisting of proteins, nucleic acids, carbohydrates, and lipids.

Claim 57 (withdrawn): The method of claim 56, wherein the target is a receptor.

Claim 58 (withdrawn): The method of claim 57, wherein the target is a membrane-bound receptor.

Claim 59 (withdrawn): The method of claim 41, further comprising inputting data for a solvent or matrix containing the target and/or compound that interacts with the target into the equations of motion.

Claim 60 (withdrawn): The method of claim 59, wherein the matrix is a phospholipid membrane.

Claim 61 (withdrawn): The method of claim 41, wherein the solvent is an aqueous solvent.

Claim 62 (withdrawn): The method of claim 41, wherein the solvent is an organic solvent.

Claim 63 (withdrawn): The method of claim 41, wherein the data comprises the identity of components of the compound.

Claim 64 (withdrawn): The method of claim 63, wherein the data comprises the identity of atoms of the compound.

Claim 65 (withdrawn): The method of claim 41, wherein the data comprises X-ray crystallographic data.

Claim 66 (withdrawn): The method of claim 41, further comprising inputting an environmental factor into the equations of motion.

Claim 67 (withdrawn): The method of claim 41, wherein the environmental factor is the temperature or pressure at which interaction between the compound and target is to be determined.

Claim 68 (withdrawn): The method of claim 41, wherein the library of compounds comprises at least 10^{10} members.

Claim 69 (withdrawn): The method of claim 41, wherein the library of compounds comprises at least 10^{50} members.

Claim 70 (withdrawn): The method of claim 41, wherein the integrating step determines a binding affinity between the compound and the target and the comparing step compares the binding affinities of different compounds with the target, and the synthesizing step synthesizes the compound with the highest affinity for the target.

Claim 71 (withdrawn): The method of claim 41, wherein the integrating step determines an interaction between the compound and the target that indicates the compound binds to the target with an affinity of at least 10^9 M^{-1}.

Claim 72 (withdrawn): The method of claim 41, wherein the integrating step determines an interaction between the compound and the target that indicates the compound transduces a signal through the target.

Claim 73 (withdrawn): The method of claim 41, wherein the compounds are potential detergents and the integrating step determines an interaction between the compound and the target that indicates the compound denatures the target.

Claim 74 (withdrawn): A method of evolving a protein to have a desired functional property comprising:

(a) selecting a model for a reference form of the protein, the model having equations of motion for the protein;

(b) inputting data for an amino acid substitution of the protein into the equations of motions;

(c) integrating said model equations with an L-stable integrator in large time steps so as to obtain a calculation of the motions of the protein with the amino acid substitution;

(d) repeating steps (b) and (c) for additional amino acid substitutions;

(e) comparing the motions of proteins with different amino acid substitutions;

(f) synthesizing a protein with an amino acid substitution selected based on the comparison.

Claim 75 (withdrawn): The method of claim 74, further comprising testing the selected synthesized protein for a desired functional property.

Claim 76 (withdrawn): The method of claim 74, wherein the desired functional property is capacity to bind a target.

Claim 77 (withdrawn): The method of claim 74, wherein the desired functional property is an enzymatic activity.

Claim 78 (withdrawn): A method of humanizing an immunoglobulin chain, comprising:

(a) providing an amino acid sequence for an immunoglobulin chain comprising CDR regions from a mouse antibody and variable region frameworks from a human antibody;

(b) selecting a model for the immunoglobulin chain the model having equations of motion for the immunoglobulin chain;

(c) integrating the model equations with an L-stable integrator in large time steps so as to obtain a calculation of the motions of the immunoglobulin chain;

(d) determining from the model which amino acid residues in the variable framework region interact with the CDR regions;

(e) substituting one or more of the amino acid residues in the variable framework region that interact with the CDR regions with corresponding amino acids from the mouse antibody;

(f) synthesizing the immunoglobulin chain including the one or more amino acid residues.

Claim 79 (withdrawn): The method of claim 78, further comprising testing the synthesized immunoglobulin chain for binding to a target.

Claim 80 (withdrawn): A method of calculating behavior or properties of one or more molecules in specified circumstances, comprising

(a) mathematically modeling said molecules and their environment, said model having equations of motion for said molecules expressed in a reduced set of coordinates; and

(b) numerically integrating said model equations with an implicit integrator using large timesteps, said integrator having stability properties and stepsize selection methods permitting the use of said large timesteps in calculating said behavior or properties with accuracy sufficient for said circumstances.

Claim 81 (withdrawn): The method of claim 80 wherein said large timesteps comprise an interval of at least 200 femtoseconds.

Claim 82 (withdrawn): The method of claim 80 wherein said integrating step is performed with varying timesteps.

Claim 83 (withdrawn): The method of claim 82 wherein said varying timesteps comprise one of at least 200 femtoseconds.

Claim 84 (withdrawn): The method of claim 80 wherein said stepsize selection method comprises accuracy estimation.

Claim 85 (withdrawn): The method of claim 80 wherein said stepsize selection method comprises convergence requirements.

Claim 86 (withdrawn): The method of claim 80 wherein said stepsize selection method comprises energy dissipation requirements.

Claim 87 (withdrawn): The method of claim 80 wherein said integrator has the L-stability property.

Claim 88 (withdrawn): The method of claim 80 wherein said integrator comprises an integrator from the group comprising of L-stable members of order 2 or greater of the Radau, SDIRK, SIRK, or Rosenbrock families of integration methods.

Claim 89 (withdrawn): The method of claim 87 wherein said L-stable integrator comprises the Radau5 integration method.

Claim 90 (withdrawn): The method of claim 80 wherein said integrator comprises an integrator from the group comprising DASSL and other implicit multistep methods designed for stiff or differential-algebraic systems.

Claim 91 (withdrawn): The method of claim 80 wherein said coordinates are reduced by the use of one or more rigid bodies comprising two or more atoms each, and internal coordinates.

Claim 92 (withdrawn): The method of claim 91 wherein the internal coordinates comprise torsion angles.

Claim 93 (withdrawn): The method of claim 80 wherein said coordinates are reduced by the use of substructuring a molecule into rigid or flexible subcomponents.

Claim 94 (withdrawn): The method of claim 80 wherein said environment comprises a vacuum.

Claim 95 (withdrawn): The method of claim 80 wherein said environment comprises a solvent.

Claim 96 (withdrawn): The method of claim 95 wherein said solvent comprises an implicit representation.

Claim 97 (withdrawn): The method of claim 96 wherein said implicit solvent comprises non-uniform solvent properties such as membrane regions.

Claim 98 (withdrawn): The method of claim 80 wherein said circumstances comprise a dynamic simulation.

Claim 99 (withdrawn): The method of claim 98 wherein said circumstances comprise Newtonian dynamics.

Claim 100 (withdrawn): The method of claim 98 wherein said circumstances comprise Langevin dynamics.

Claim 101 (withdrawn): The method of claim 80 wherein said circumstances comprise the search for a reduced energy state of said molecules.

Claim 102 (withdrawn): The method of claim 101 wherein said search comprises only the local energy basin of the starting configuration.

Claim 103 (withdrawn): The method of claim 101 wherein said search comprises energy basins other than the local basin of the starting configuration.

Claim 104 (withdrawn): The method of claim 80 wherein said molecule comprises a single biopolymer in a non-native circumstance, and said properties comprise the folded native structure of said biopolymer.

Claim 105 (withdrawn): The method of claim 104 wherein said biopolymer is a polypeptide or protein.

Claim 106 (withdrawn): The method of claim 104 wherein said biopolymer is a nucleic acid.

Claim 107 (withdrawn): The method of claim 80 wherein said molecules comprise a target molecule and a ligand molecule where said behavior comprises binding of ligand to target or said properties comprise binding affinity, binding preferences, binding rates or other binding properties.

REMARKS/ARGUMENTS

The Examiner restricted the claims in the present application and has required election of one of the following inventions under 35 U.S.C. §121: Group I, Claims 1-23 and 35-40; Group II, Claims 24-34; Group III, Claims 41-73; Group IV, Claims 74-77; Group V, Claims 78-79. The Office action also included a Specie Election Requirements, which as applied to the Claims of elected Group I, requires election of a specific L-Stable integrator.

Applicant hereby elects, without traverse, to engage prosecution of Group I, Claims 1-23 and 35-40; and with respect to the election of specie requirement, elects to begin prosecution with the Radau5 implicit integrator.

Claims 24 through 34 and 41 through 107 have been withdrawn from consideration by the Examiner's restriction requirement. Further, Claims 7, 16, 20 and 21 have been withdrawn from consideration by the Examiner's election of specie requirement. Claims 1, 13, 15, and 35 have been amended to correct obvious typographical errors (Claims 13 and 35) and to introduce limitations from dependent claims to address the Examiner's election of specie requirement (Claims 1, 13, 15, and 35); specifically, Claims 1, 13, 15, and 35 have been amended to delete "L-stable" and replace it with "Radau5". This amendment was done solely to comply with the election of specie requirement under 35 U.S.C. §121, and was not done for any reason related to patentability of the invention under 35 U.S.C. §101, 102, 103 or 112.

Should one or more generic claims be held allowable, Applicant reserves the right to re-introduce claims, directed to unelected species, for consideration by the Examiner. Applicant also reserves the right to file divisional application(s) to any or all of the non-elected inventions.

The date for reply under the shortened statutory period of one month from mailing of the October 23, 2003, Office action is November 23, 2003, which, falling on a Sunday, extends the period for response to Monday, November 24, 2003.

No fees are believed to be due with this response. However, should the Commissioner determine that fees are due, the Commissioner is hereby authorized to charge any fees (or credit any overpayment) in connection with this Response to Deposit Account No. 50-2599.

Respectfully submitted,

Charles K. Sholtz
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Date: November 24, 2003

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